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VALUE IN HEALTH

Quantifying the Decrement in Utility from Perceived Side Effects of Combination Antiretroviral Therapies in Patients with HIV

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ABSTRACT

Background: The decrement in utility attributable to side effects from combination antiretroviral therapy (CART) is unknown and likely to influence clinical decisions regarding CART initiation and cost-effectiveness.

Objective: To quantify the decrement in utility attributable to side effects from CART.

Methods: We estimated SF-6D utilities (quality-of-life weights on a scale from 0.29 [worst possible health] to 1.00 [perfect health]) from SF-12 scores among patients with HIV in the Veterans Aging Cohort Study by using a published and validated conversion algorithm. We then compared utilities among patients who: 1) did not have bothersome symptoms while taking CART; 2) had bothersome symptoms that they thought might be due to CART; and 3) had bothersome symptoms that they were confident were due to CART; we controlled for other characteristics known to influence quality of life and stratified analyses by CD4 count.

Results: Among 1864 patients with available data, symptoms perceived to be attributable to CART were associated with a mean (95% confidence interval) decrement in utility of 0.06 (0.05, 0.08) points in univariate analyses and 0.08 (0.06, 0.10) in multivariable analyses, clinically significant differences that are comparable to utility decrements reported for partial impotence or mild angina. Other significant predictors of changes in SF-6D utilities were hazardous alcohol consumption, recent drug use, cigarette smoking, homelessness, and African American race ($R^2 = 0.12$). Stratifying by CD4 count, symptoms attributable to CART side effects decreased utility by 0.03 to 0.08 points.

Conclusions: Symptoms perceived to be related to CART are associated with a substantial decrement in utility.

Keywords: cost-effectiveness analysis, quality of life, utility assessment.

Introduction

Combination antiretroviral therapy (CART) has transformed HIV from a rapidly fatal condition to a chronic disease, and their benefits overwhelmingly exceed their harms for individuals with pretreatment CD4 counts below 200 cells/μl [1]. Nevertheless, individuals with CD4 counts greater than 200 cells/μl have a lower imminent risk of AIDS-related death, and it remains unclear whether the benefits of CART would exceed the harms for such patients. Side effects from CART are common and clinically significant even with newer and better-tolerated CART regimens [1], and therefore are likely to be an important component of any aggregate harm from CART.

Quantitatively weighing the harms and benefits of CART is important because their relative balance may inform unresolved clinical questions such as the optimal time for beginning CART, and may also affect the cost-effectiveness of CART. Nevertheless, quantifying the burden from CART side effects has been elusive. Although several studies have measured quality-of-life changes following CART initiation [2–5], their design was unable to distinguish between quality-of-life changes due to side effects and quality-of-life changes due to reductions in disease severity.

Because quantifying harms attributable to CART requires isolating its negative effects on quality of life from its other, more positive, consequences, we sought to investigate the relationship between side effects and quality of life associated with CART. We used data from the Veterans Aging Cohort Study (VACS), a large national study of veterans under care for HIV that incorporates a thorough inventory of questions regarding symptom burden and quality of life.

Methods

We first describe how we identified patients with substantial side effects from CART. We then explain how we measured quality of life. Finally, we describe how

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we compared the quality of life among patients with and without side effects from CART, controlling for other characteristics that are important predictors of quality of life.

Identifying Patients with Side Effects from CART

Veterans Aging Cohort Study is an ongoing eight-site prospective study of HIV-positive and matched HIV-negative veterans in care that is designed to assess how an aging HIV population is impacted by risk factors, comorbidities, and extended exposure to CART. It is designed to measure morbidity as well as mortality, and therefore includes detailed surveys on symptom burden and quality of life [6]. HIV-positive participants were asked to complete the HIV Symptom Index [7], a validated instrument that queries respondents about 20 symptoms common among patients with HIV, with possible responses of "I do not have this symptom," "[I have it but] it doesn't bother me," "it bothers me a little," "it bothers me," and "it bothers me a lot." After completing the HIV Symptom Index, participants were also asked to complete a single item that queried beliefs about whether their symptoms were attributable to antiretroviral medications ("Do you think your symptoms are caused by the drugs you take to treat your HIV infection?"). Surveys were completed between June 2002 and September 2004.

We sought to distinguish patients with substantial side-effect burdens from patients with few or no side effects. We reasoned that patients with substantial side-effect burdens were those who: 1) endorsed one or more of the symptoms in the HIV Symptom Index; (2) endorsed a high degree of burden from at least one of these symptoms (i.e., "it bothers me" or "it bothers me a lot"); and 3) reported that symptoms were possibly or definitely attributable to CART. For this analysis, we considered patients who met all the three criteria as having side effects from CART, whereas all other patients were considered not to have side effects from CART. We separately analyzed data from patients reporting "possible" attribution of symptoms to CART versus patients reporting "definite" attribution of symptoms to CART.

Measuring Quality of Life

All patients in VACS completed the Medical Outcomes Study SF-12, a widely used multidimensional health status instrument [8]. Because our ultimate aim was to yield results that could quantify the benefits and harms associated with CART, we assessed quality of life using the construct of "utility," a generic unidimensional measure commonly used to represent quality of life in decision analysis and cost-effectiveness analysis. Brazier and Roberts [9] derived and validated a robust conversion algorithm that estimates utilities based on a six-dimensional subset of SF-12 questions—the SF-6D—and we used this conversion algorithm to estimate a utility for each VACS subject who completed the SF-12. Although the SF-6D is scaled on a restricted range, from 0.29 (worst possible health) to 1.00 (perfect health), it may have similar discriminatory power compared to other approaches for eliciting utilities [10].

Comparing Quality of Life of Patients with and without Side Effects

We then compared the utilities of subjects who: 1) did not have bothersome symptoms while taking CART; 2) had bothersome symptoms that they thought might be due to CART; and 3) had bothersome symptoms that they were confident were due to CART. We performed univariate analyses as well as multivariable analyses that controlled for other patient characteristics that were likely to be associated a priori with quality of life or that have been shown to be associated with quality of life in previous reports [11–13]. Definitions of these characteristics and details about their measurement are described in more detail elsewhere [6].

We wanted to ensure that any quality-of-life changes observed could not be explained by differences in CD4 counts (i.e., patients experiencing side effects may be less adherent or have other characteristics that result in less favorable CD4 count trajectories, and the CD4 count differences rather than the side effects could lead to the observed utility discrepancies). For this reason, we performed analyses stratified by CD4 count (<50, 50–199, 200–349, 350–499, and = 500 cells/μl). We used the CD4 count closest to the survey date within a window of 6 months. Additionally, to explore the degree to which decrements in utility from CART varied by major demographic factors, we also performed similar analyses stratified by age and race. Because of insufficient power to perform stratified multivariable analyses, we limited the stratified analyses to univariate analyses.

Statistical Methods

To explore the adjusted association between CART and utility, we used generalized linear models with the linear portion log-transformed, and the errors assumed to be normally distributed. The response variable was utility and the predictor variables were age, sex, race, hazardous alcohol consumption (defined as an AUDIT score >8) [14], homelessness in the 4 weeks before the survey, substance abuse in the past year, cigarette smoking in the past week, depression, and type of CART (protease-inhibitor–based vs. non-nucleoside-reverse-transcriptase-inhibitor–based vs. triple-nucleoside–based). *P*-values less than 0.05 were considered to be statistically significant. We performed all analyses by using SAS statistical software, version 9.1 (SAS Institute, Cary, NC). We estimated the R^2 for

the model using a published method for common nonlinear regression models [15].

Results

Patients in VACS were generally older (median age, 50.0 years), poorer (median household income = $25,000/year), more likely to be non-White (73%), and more likely to be male (97%) compared to those in other observational HIV cohorts in the United States. Substantial proportions of patients were hazardous drinkers (18%), illicit drug users (28%), or homeless (9%).

Of 2099 HIV-infected patients enrolled in VACS at the time of this analysis, 2066 (98%) completed patient surveys related to symptoms, and 1864 (89%) had complete data available for analysis. Approximately two-thirds (66%) had perceived side effects from CART. Of those, approximately half were unsure about whether these symptoms were attributable to medications (39% of all surveyed), whereas the remainder (28% of all surveyed) were confident that symptoms were attributable to medications.

In univariate analyses, patients with symptoms had significantly lower utilities than patients without symptoms. Compared to patients reporting no symptoms, mean utilities were 0.06 (95% confidence interval [CI] 0.04–0.07) points lower among patients who had symptoms but were unsure whether they were due to CART. Similarly, utilities were on average 0.06 (95% CI 0.05–0.08) points lower for patients who were confident that their symptoms were due to CART, as compared to asymptomatic patients. Race, age, and CD4 cell count were variably associated with changes in utility from CART.

Multivariable analyses confirmed the effect of perceived CART side effects on utility (Table 1). Symptoms possibly attributable to side effects exacted a mean decrement in utility of 0.09 (95% CI 0.07–0.10) points, whereas symptoms definitely attributable (according to patients) to CART side effects carried a decrement in utility of 0.08 (95% CI 0.06–0.10) points. Other statistically significant factors associated with SF-6D utilities were hazardous alcohol consumption, drug use, smoking, homelessness, and race ($R^2 = 0.12$). Type of antiretroviral regimen was not significantly associated with utility.

In stratified analyses (Table 2), perceived side effects continued to have a significant impact on utility in all CD4 strata except for the CD4 < 50 cells/μl category, with mean decrements in utility ranging from 0.03 to 0.08 points for patients who were confident that their symptoms were due to CART side effects. While this was generally a robust finding, the association was attenuated in the lowest CD4 stratum. Decrements in utility did not appear to vary greatly by age or by race (Table 2).

Table 1 Multivariable analysis of utility for HIV-positive subjects (N = 1864)

Characteristic	Effect (95% confidence interval)*	*P*-value
Intercept	−0.27 (−0.30 to −0.24)	<0.0001
Symptoms definitely attributable (according to the patient) to CART	−0.08 (−0.10 to −0.06)	<0.0001|
Symptoms possibly attributable (according to the patient) to CART	−0.09 (−0.10 to −0.07)	<0.0001
Age > 50 years	−0.01 (−0.03 to 0.00)	NS
Female sex†	−0.00 (−0.05 to 0.05)	NS
Hazardous alcohol consumption‡	−0.00 (−0.01 to −0.00)	<0.0001
Recent drug use	−0.02 (−0.04 to −0.01)	0.0122
Cigarette smoking	−0.03 (−0.05 to −0.02)	<0.0001
Homelessness within last 4 weeks	−0.06 (−0.09 to −0.03)	<0.0001
African American race	0.03 (0.02 to 0.05)	0.0001
CART containing PIs§	−0.01 (−0.02 to −0.01)	NS
CART containing NNRTIs§	0.01 (−0.01 to 0.02)	NS

*Negative values connote disutility (worse quality of life).
†Effect was −0.002.
‡Effect was −0.004.
§Referent category was triple-nucleoside–based therapy.
CART, combination antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NS, not significant at $P < 0.05$; PI, protease inhibitor.

Discussion

In our national study of veterans with HIV, we detected substantial decrements in quality of life that were thought by patients to be due to side effects from CART. The decrement of approximately 0.08 utility units is clinically meaningful (e.g., greater than 0.04 utility units, the minimally important difference reported for the SF-6D across 11 studies) [16], substantial (e.g., similar to the decrement in utility of partial impotence or mild angina [17] and comparable to the decrement in utility associated with homelessness in our analysis), but not overwhelming (e.g., less than the decrement in utility of complete impotence or moderate angina [17]). The decrement in utility associated with CART was fairly robust across different patient subgroups.

While the benefits of CART are comparatively easy to quantify because of the abundance of relevant data, the harms associated with CART are less certain. Published studies reporting quality-of-life changes associated with CART have been unable to disaggregate the impact of its side effects from its benefit with regards to HIV progression. In this study, we attempted to isolate the impact of perceived side effects of CART. The relative similarity of our results across CD4 strata suggests that the decrements in utility that we found do not result from differences in disease stage. That is, our results are unlikely to reflect the possibility that patients with side effects have worse CD4 levels as an explanation for lower utilities. Interestingly, decrements in utility of symptomatic patients who were unsure whether their symptoms were due to CART side effects were similar to those of patients who were confident that their symptoms were due to CART.

Table 2 Associations of SF-6D utilities with symptoms, stratified by CD4 count, age, and race/ethnicity

	N	Utility of subjects with no symptoms	Utility change in symptomatic patients uncertain whether their symptoms are due to CART side effects (mean, 95% CI)	Utility change in symptomatic patients confident that their symptoms are due to CART side effects (mean, 95% CI)
CD4 count (cells/μl)				
0–49	94	0.66	−0.00 (−0.06 to 0.07)	−0.03 (−0.10 to 0.05)
50–199	365	0.73	−0.07 (−0.10 to −0.04)	−0.05 (−0.09 to −0.02)
200–349	486	0.72	−0.04 (−0.07 to −0.01)	−0.04 (−0.07 to −0.01)
350–499	435	0.74	−0.07 (−0.10 to −0.04)	−0.07 (−0.10 to −0.04)
500+	485	0.75	−0.08 (−0.10 to −0.05)	−0.08 (−0.10 to −0.05)
Age (year)				
<35	90	0.78	−0.06 (−0.12 to −0.01)	−0.03 (−0.10 to 0.04)
35–44	462	0.75	−0.06 (−0.09 to −0.03)	−0.07 (−0.10 to −0.04)
45–54	924	0.72	−0.06 (−0.08 to −0.04)	−0.06 (−0.08 to −0.04)
55–64	421	0.73	−0.07 (−0.10 to −0.04)	−0.05 (−0.08 to −0.02)
65+	107	0.78	−0.07 (−0.13 to −0.02)	−0.07 (−0.13 to −0.01)
Race/ethnicity				
Black	1289	0.74	−0.07 (−0.08 to −0.05)	−0.06 (−0.07 to −0.04)
White	461	0.71	−0.05 (−0.08 to −0.02)	−0.05 (−0.08 to −0.02)
Hispanic	202	0.72	−0.04 (−0.09 to 0.01)	−0.05 (−0.10 to 0.00)
Other	52	0.74	−0.11 (−0.20 to −0.02)	−0.10 (−0.20 to −0.00)
SF-12 score				
PCS	2047	45.33	−3.54 (−4.76 to −2.32)	−3.68 (−4.80 to −2.56)
MCS	2047	32.16	1.13 (0.15 to 2.11)	0.85 (−0.22 to 1.91)

CART, combination antiretroviral therapy; CI, confidence interval; MCS, mental component score; PCS, physical component score.

Our methods have several limitations. Even though we controlled for a comprehensive set of potential confounders, our cross-sectional approach precludes inferring causality. We based our definition of side effects on patients' perceptions of whether symptoms were in fact attributable to CART. This assumption has not been well studied, and the validity of our work may be lessened if patients misattributed their symptoms. The landscape of HIV treatment changes rapidly, and our findings may not apply to the newest CART regimens. Finally, we estimated utilities based on SF-12 scores using the SF-6D rather than directly eliciting them using a technique such as the standard gamble or time trade-off. This method produces estimates that are compressed into a comparatively narrow range (0.29–1.00), with lower valuations for favorable health states and higher valuations for unfavorable health states compared to other approaches [18–20]. Nonetheless, decrements in utility estimated using the SF-6D were similar to decrements in utility estimated using other instruments (e.g., EuroQol EQ-5D) in a representative sample of 11,421 US adults across a wide range of conditions and risk factors, increasing the likelihood that our results are generalizable [10]. Furthermore, our study's limitations must be interpreted in the context of its strengths, which stem from its large sample size and its substantial augmentation of existing literature on CART and quality of life. Other than its sex distribution (predominantly male), our cohort is more representative of the HIV epidemic in the United States than many other large observational cohorts [21]. Our results may be a useful tool for investigators who wish to quantify harms and benefits from CART for clinical care or for cost-effectiveness analysis.

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